REMARKS

In a non-final Office Action mailed July 17, 2006, the Examiner maintained and made final a requirement for restriction and rejected the claims under 35 U.S.C. §§ 102(a) and 112 (first paragraph). Applicants respond to each rejection below. In view of the amendment noted above and the arguments below, Applicants respectfully request reconsideration of the merits of this application.

Rejections Under 35 U.S.C. § 102(a)

Claims 1-8 and 12-13 are rejected under 35 U.S.C. § 102(a) as being anticipated by Caspi, A, *et al.*, "Role of genotype in the cycle of violence in maltreated children," Science 297:851-854 (2002). The Examiner alleges that Caspi *et al.* anticipates the pending claims by teaching a method of determining whether a subject is predisposed to a disorder phenotype by virtue of carrying a particular allele of monoamine oxidase A (MAOA) and by virtue of experiencing a particular environmental risk factor.

Applicants' claims are not properly rejected under 35 U.S.C. § 102(a) over a disclosure of Applicants' own work less than one year before the application filing date. MPEP § 2132.01; *see also In re Katz*, 687 F.2d 450, 215 USPQ 14 (CCPA 1982). Caspi *et al.* was published on August 2, 2002, less than one year before the July 11, 2003 application filing date. In support of Applicants' assertion that Caspi *et al.* describes Applicants' own work, Applicants enclose a 37 C.F.R. § 1.132 Declaration by the named inventors explaining the involvement of the non-inventor authors of Caspi *et al.* in the research underlying both the paper and the application. In view of these remarks and the enclosed Declaration, Applicants respectfully request reconsideration of this rejection as applied to Claims 1-8 and 12-13.

Rejections Under 35 U.S.C. § 112, first paragraph

The Examiner rejected Claims 1-13 under 35 U.S.C. § 112, first paragraph as failing to meet the enablement requirement for four reasons. Applicants respectfully maintain that a skilled artisan can readily practice the claims for the reasons noted below. At the outset, Applicants amend Claim 1 to recite that the subject is a human subject, thereby rendering moot the stated basis for rejection that the specification fails to enable claims embracing methods of predicting predisposition to a mental disorder phenotype in a non-human subject.

Also, to highlight a fundamental advance embodied in the claims but overlooked in the Office Action, Applicants also respond at the outset to the Examiner's comments at pages 7 and 8 near the end of the Office Action. The Examiner cites six scientific articles that allegedly demonstrate a high unpredictability regarding the association of MAOA polymorphisms with mental disorder phenotypes. However, each cited document addresses only direct gene-to-disorder effects (i.e. G → D; wherein G = gene and D = disorder). No cited document considers the conditioning effect of environmental risk factors. A key inventive concept not heretofore shown relates to the discovery of a conditional association of an environmental risk factor with a genotype in mediating the mental disorder phenotype. Applicants demonstrate that the at-risk allele of MAOA is only associated with the mental disorder phenotypes in individuals that have endured a pathogenic environmental risk (i.e. G x E → D; wherein G = gene, D = disorder and E = environmental risk factor). Applicants harness the predictive power of this demonstration by assessing a predisposition to the mental disorder phenotypes so that, where possible, such environmental risks can be avoided.

The Examiner alleges that the specification fails to enable claims embracing methods that consider other polymorphisms within MAOA or polymorphisms in other genes that may be linked to expression of MAOA and the related mental disorder phenotypes. Applicants respectfully disagree. In making the claimed invention, Applicants demonstrated that low activity level conditioned by experience (or risk of experience) of an environmental risk factor permits assessment of a predisposition to a mental disorder phenotype. The art is replete with studies of high and low MAOA activity level and a skilled artisan can readily determine whether a subject has a high or low activity level. Even where an allelic (i.e., nucleotide-level) cause of a low activity level is not specified, the skilled artisan understands that an at-risk allele (here, an at-risk allele of a gene that encodes MAOA enzyme having a low activity level in the brain of the subject) underlies the cause. The gene that encodes MAOA is well-known. Routine methods are known for assaying MAOA activity and genetic aberrations such as truncations, deletions, substitutions, repeats in the MAOA gene. A skilled artisan can readily measure MAOA activity and can readily ascertain whether the activity is low or high. Where a low MAOA activity level is observed, the skilled person can identify an underlying genetic aberration and can design a diagnostic test for the aberration. Paragraph [00021] of the Specification provides additional guidance on contemplated polymorphisms. To limit applicants to a single polymorphism unduly limits Applicants claims and understates the level of skill in the art.

The Examiner further alleges that the specification fails to enable claims embracing methods that predict predisposition to additional phenotypes having an association with an at-risk allele of a gene that encodes MAOA. Applicants respectfully disagree. The claims embrace mental disorder phenotypes having an association with an at-risk allele of a gene that encode MAOA. The mental disorder phenotypes can be selected from behavioral, emotional or cognitive disorder phenotypes, all of which are defined according to the Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition (DSM-IV; published by the American Psychiatric Association), which was incorporated into the application by reference. *See* paragraph [00015]. Like the MPEP for a Patent Examiner, DSM-IV is a 'bible' for any professional in the United States or around the world who makes psychiatric diagnoses. Applicants submit that a skilled person refers to the DSM-IV for guidance in understanding the scope of behavioral, emotional or cognitive disorder phenotypes and association of such phenotypes with an at-risk allele of the gene that encodes MAOA (i.e., associated with low activity level). As noted above, the skilled person can readily determine whether a subject has a low MAOA level in the brain and, if so, the nature of the at-risk allele. Neither step demands undue experimentation.

The Examiner still further alleges that the specification fails to enable claims that embrace methods that relate other pathogenic environmental risk factors to the related mental disorder phenotypes. In the relevant fields of psychology and psychiatry -- extraordinarily fluid fields of study -- the skilled artisan understands that absolute certainty can neither be required nor achieved, and the artisan therefore accepts some uncertainly as to the precise impact of environmental risk factors. As such, the skilled person is accustomed to spending time and effort discovering environmental risk factors associated with particular mental disorder phenotypes. Undue experimentation is therefore not called for when the skilled artisan identifies candidate pathogenic environmental risk factors from scientific literature or from the DSM-IV. As noted above, the DSM-IV provides art-accepted standards and guidance for discovering environmental risk factors. Moreover, "[a] pool of candidate environmental risk factors is available for outcomes such as substance abuse (Heath & Nelson, 2002), the antisocial disorders (Loeber & Farrington), depression (Kendler, Gardner & Prescott, 2002), and even schizophrenia spectrum disorders (Tsuang, Stone & Faraone, 2001; van Os, Krabbendam, Myin-Bermeys & Delespaul, 2005)." *See* Moffitt T, *et al.*, "Measured gene-environment interactions in psychopathology: concepts, research strategies,

and implications for research, intervention, and public understanding of genetics," Persp. Psychol. Sci. 1:5-27 (2006).

Applicants further note that the landmark study upon which the application was based has now been replicated by at least five other groups. Kim-Cohen, J, *et al.*, "MAOA, maltreatment, and gene-environment interaction predicting children's mental health: new evidence and a meta-analysis," Mol. Psychiatry. 11:903-913 (2006) (copy provided) summarize these replicated studies. Of particular interest is the reported finding that Applicants' methods produced consistent results in each of the studies discussed therein.

In further support of Applicants' assertion that the application enables the skilled person to practice the claimed invention, Applicants note that the basic inventive concept has successfully identified two other mental disorder phenotypes conditioned upon pathogenic environmental risks. First, Applicants used the disclosed inventive concept to characterize a link between a functional polymorphism in a promoter region of a serotonin transporter gene (5-HTTLPR) that moderates the influence of stressful life events on depression. *See* Caspi A, *et al.*, "Influence of life stress on depression: moderation by a polymorphism in the 5-HTT gene," Science 301:386-389 (2003). Applicants also used the same inventive concept to characterize a link between a functional polymorphism in a catechol-O-methyltransferase gene that moderates the influence of cannabis use on psychosis. *See* Caspi A, *et al.*, "Moderation of the effect of adolescent-onset cannabis use on adult psychosis by a functional polymorphism in the catechol-O-methyltransferase gene: longitudinal evidence of a gene X environment interaction," Biol. Psychiatry. 57:1117-1127 (2005).

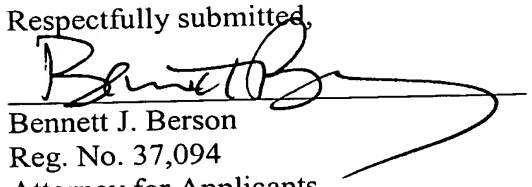
In view of these remarks, Applicants respectfully request reconsideration of this rejection as applied to Claims 1-13.

Fees

A petition for a three-month extension of time accompanies this response so that it will be deemed to have been timely filed.

No other extension of time is believed due, but should any other extension be due, in this or any subsequent response, please consider this to be a petition for the appropriate extension and a request to charge the extension fee to Deposit Account No. 17-0055. No additional fees are believed due; however, if any fees are due, in this or any subsequent response, please charge Deposit Account 17-0055.

Respectfully submitted,



Bennett J. Berson
Reg. No. 37,094
Attorney for Applicants
QUARLES & BRADY LLP
P.O. Box 2113
Madison, WI 53701-2113

TEL (608) 251-5000
FAX (608) 251-9166